PAIN-REDUCING EFFECTS OF FIBROBLASTS AND TREATMENT OF PAIN

[0001] This application claims priority to U.S. Provisional Patent Application Ser. No. 62/666,828, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] Embodiments of the disclosure regard at least the fields of cell biology, molecular biology, biochemistry, and medicine.

BACKGROUND

[0003] Lower back pain (LBP), causes significant impact personally and socially, affecting 70 to 80% of adults least once in a lifetime [1]. In 1998, about 26.3 billion dollars were expended due to LBP in United States [2]. Back pain (BP) is generally self-limited and positive and patients undergoing acute BP may usually become better in one month or can return to work [3, 4]. However, 2 to 7% of the patients show the progress into chronic BP and chronic or regenerative BP may cause 75 to 85% of absence from works [5-7]. Accordingly, in case of occurring acute BP, it is important to apply a method of treating while minimizing side effects to thus relieve pains, which in turn improves functionality, reduces a rate of absence and suppress the progress into chronic BP. Treatment of LBP generally includes prescription of an analgesic agent, for example, acetaminophen, or non-steroid anti-inflammatory drugs (NSAIDs) and also encouraging a patient to continuously retain daily activity [8, 9]. NSAIDs are effective for curing BP a short period of time and, in an aspect of relieving pains, more superior over acetaminophen [10]. In most general, intramuscular application of diclofenac is a method of curing acute pains however, using NSAID often causes side effects in the stomach (and intestines) [11]. There is currently an increasing concern about safety of cyclooxygenase-2 selective NSAIDs for cardiovascular diseases, in particular, thrombotic diseases such as acute myocardial infarction, unstable angina pectoris, cardiac arrest, sudden (cardiac) death [12]. The disclosure provides a means to overcome pain, particularly in individuals with LBP through the intradiscal administration of fibroblasts or derivatives of fibroblasts.

BRIEF SUMMARY

[0004] The present invention is directed to methods and compositions related to the treatment or prevention of pain. In particular embodiments, any type of pain is treated or prevented upon administration of fibroblasts and/or fibroblast derivatives such as extracts of the fibroblasts, lysates of the fibroblasts, and/or nucleic acid compositions thereof.

[0005] In particular embodiments the individual has been determined to have a need for the treatment of pain, and in specific embodiments a medical practitioner provides the fibroblasts and/or fibroblast derivatives for the treatment of pain specifically. The delivered fibroblasts and/or fibroblast derivatives may or may not have another therapeutic or preventative aspect in vivo.

[0006] The disclosure pertains to the field of pain management, more specifically, the disclosure pertains to the field of utilizing fibroblasts and/or fibroblast derivatives to ameliorate pain by means of administering the fibroblasts and/or fibroblast derivatives into an individual in need of therapy. More specifically, the disclosure encompasses the use of intradiscally-administered fibroblasts to reduce pain, in particular discogenic pain.

[0007] In one embodiment, there is a method of treating or preventing pain in an individual, comprising the step of administering to the individual an effective amount of fibroblasts and/or derivatives thereof and/or conditioned media from culture of the fibroblasts. The administration may be local or systemic to the individual. The administration may be to the spine of the individual, and the administration may be intradiscally in the individual. In some cases, the pain is acute or chronic. The individual may be receiving an additional treatment, such as for pain. The pain may be of any kind, including at least a) neuropathic pain; b) nociceptive pain; c) phantom pain; d) psychogenic pain; e) incident pain; f) breakthrough pain; g) discogenic pain; h) idiopathic pain; or i) a combination thereof.

[0008] In some embodiments, the fibroblast derivative comprises lysate and/or exosomes, and the exosomes may be obtained following culture of the fibroblasts under suitable conditions.

[0009] The fibroblasts may express CXCR-4; CD-271; FGF-1 receptor; SSEA-3; CD10; CD13; CD44; CD73; CD90; TNF-alpha receptor-1; toll like receptor 4; and/or the receptor for acetylated end products (RAGE). The fibroblasts may be cultured under hypoxia. When the fibroblasts are cultured under hypoxia they may secrete one or more factors selected from the group consisting of a) MCP-1; b) MIP1beta; c) IL-6; d) IL-8; e) GCP-2; f) HGF; g) KGF; h) FGF; i) HB-EGF; j) BDNF; k) TPO; l) RANTES; m) TIMP1; and n) a combination thereof.

[0010] Exosomes from fibroblasts may be administered instead of or in addition to the fibroblasts. The conditioned media and the fibroblasts may be administered concurrently or at separate times. The exosomes and the fibroblasts may be administered concurrently or at separate times.

[0011] In specific embodiments, the exosomes express one or more markers selected from the group consisting of CD63, CD9, MHC I, CD56, and a combination thereof.

[0012] Embodiments of the disclosure include isolated exosomes produced from fibroblasts cultured in vitro under hypoxic conditions. The exosomes may express one or more markers selected from the group consisting of CD63, CD9, MHC I, CD56, and a combination thereof. Any exosomes may be formulated as a pharmaceutical composition.

[0013] The foregoing has outlined rather broadly the features and technical advantages of the present disclosure in order that the detailed description that follows may be better understood. Additional features and advantages will be described hereinafter which form the subject of the claims herein. It should be appreciated by those skilled in the art that the conception and specific embodiments disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present designs. It should also be realized by those skilled in the art that such equivalent constructions do not depart from the spirit and scope as set forth in the appended claims. The novel features which are believed to be characteristic of the designs disclosed herein, both as to the organization and method of operation, together with further objects and advantages will be better understood from the following description when considered in connection with the accompanying figures. It is to be expressly understood, however,